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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,228	04/12/2001	Elaine L. Jacobson	NIAD-214.1 US	3352

24972 7590 07/28/2004

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,228	JACOBSON ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-33 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 3, 2003 has been entered.

Applicant's amendments filed April 7, 2003 have been entered. The cancellation of claim 34 in amendment filed APRIL 7, 2003 is acknowledged.

Claims 30-33 and 35-37 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30-33 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huber (US Patent 2,431,558) in view of Otsuka et al. (US Patent 5,151,271). Otsuka is reference of record in the previous office action mailed June 18, 2002.

Huber teaches topical administration of a vasodilator containing composition wherein the vasodilator may be C_4-C_8 alkyl nicotinate (i.e., butyl, pentyl, hexyl, heptyl, and octyl nicotinate) (See particularly col. 2, line 45-col.3, line 6; also claim 1). Huber also teaches that the topical administration of the alkyl nicotinate may increase the blood flow to tissue (See particularly col. 3, line 43-51). Huber also teaches that the weight percentage of the alkyl nicotinate may be 1-10% (See particularly claim 3). Huber especially teaches examples with around 7% of n-octyl ester of nicotinic acid (See Example 4 in col. 4).

Huber does not expressly teach the method of topical administration of the octyl nicotinate composition may enhance the oxygen delivery to tissue. Huber does not expressly teach the composition comprising butyl benzoate. Huber does not expressly teach the concentration of the active as 0.1% to 1.0%.

Otsuka et al. teaches that butyl benzoate is useful as an adjuvant agent that indirectly promotes percutaneous absorption of the active in percutaneous application (See particularly col. 4, line 45-57).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate butyl benzoate into the vasodilatation method of Huber, which would increase blood flow to the tissue and increase oxygen delivery to the tissue thereby. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate octyl nicotinate herein, in the herein claimed concentration, in the method of Huber.

One of ordinary skill in the art would have motivated to incorporate butyl benzoate into the method of Huber because butyl benzoate is known to be useful as an adjuvant agent that indirectly promotes percutaneous absorption of the active agent. Therefore, incorporate butyl benzoate into the Huber composition would have been reasonably expected to increase the absorption of any compounds of Huber, such as octyl niacin, and thereby increase its vasodilatation activity. Such vasodilatation effect and the increase of blood flow to tissue would therefore be reasonably expected to be effective to increase the delivery of oxygen to tissue. One of ordinary skill in the art would have been motivated to incorporate octyl nicotinate compounds herein in the concentration herein in the method of Huber because the optimization of result therapeutic parameters (e.g., dosage range) is obvious as being within the skill of the artisan.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, data in the instant specification, Table 2 in page 6 have been considered but are not found persuasive. The data in Table 2 merely demonstrate the duration of octyl ester is longer that of hexyl

ester. This is an expected result. This is seen to be an expected effect because the partition coefficient of octyl ester is much higher than that of hexyl ester (See Table 1 of Le et al.) No convincing and clear unexpected result is seen.

Response to Arguments

Applicant's rebuttal arguments filed APRIL 7, 2003 averring the examiner's failure to establish the connection between partition coefficients and the duration of a pharmaceutical effect have been considered, but are not found persuasive. It is well-known that drugs with a high lipid/water partition coefficient are highly fat soluble and tend to accumulate in lipid or adipose tissue. In the instant case, the lipid-soluble drug (n-octyl ester of nicotinic acid) partitions from the aqueous environment of the plasma into fat. The extraction of the drugs out of the tissue is relatively slow. (See Shargel et al., Applied Biophaceutics and Pharmacokinetics, 3rd ed., 1993, pages 77-83, especially page 77, last sentence of first paragraph, page 80-81, Section of Drug Accumulation). Therefore, comparing to n-hexyl nicotinic acid, which has a lower partition coefficient than that of n-octyl ester of nicotinic acid, n-octyl ester of nicotinic acid would be more likely to accumulate in the fat tissue and be released out of the fat tissue more slowly. Thus, the duration or the time of n-octyl ester of nicotinic acid in the body would be reasonably expected to be longer.

Applicant's rebuttal arguments filed APRIL 7, 2003 averring Huber's admission of hexyl ester being better than octyl ester and thus, the showing of n-octyl ester's longer duration should obviate the outstanding rejection under 35 USC 103 have been

considered, but are not found persuasive. First of all, the patent of Huber clearly claims that 1-10% of n-octyl ester of nicotinic acid as useful for vasodilatation (See for example, claim 3). Secondly, the record is not clear as to what Huber considers hexyl ester as better than octyl ester. It may be the side effect profile, solubility, ease of formulation, or as applicant speculate, the duration of action. Since the record is not clear, applicant's point of view as to why hexyl ester is better than octyl ester would be considered mere speculation with no factual basis and thus, not sufficient to obviate the outstanding rejection under 35 USC 103(a).

Applicant's arguments filed APRIL 7, 2003 averring compounds with more than 8 carbon in the carbon chain length not necessarily possess vasodilatation properties have been considered, but are not found persuasive. There is no claim in the instant application directed only to alkyl esters of nicotinic acid with more than eight carbons in the carbon chain. All the claims are directed to the employment of alkyl esters of nicotinic acid encompassing octyl ester of nicotinic acid. Arguments directed to unclaimed limitation are considered moot.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax

phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Patent Examiner
Art Unit 1617